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Abstract

Background: Despite the relationship of idiopathic pulmonary fibrosis (IPF) with advancing age, little is known about the epidemiology of interstitial lung diseases (ILD) in the elderly. Here we describe the diagnoses, clinical characteristics, and outcomes of patients who were elderly at the time of ILD diagnosis.

Methods: Among subjects from a prospective cohort study of ILD, elderly was defined as age $\geq$ 70. Diagnoses were derived from a multi-disciplinary review. Differences between elderly and non-elderly groups were determined using chi-square and ANOVA testing.

Results: Of the 327 subjects enrolled, 80 (24%) were elderly. The majority of elderly subjects were white and male. The most common diagnoses were unclassifiable ILD (45%), IPF (34%), hypersensitivity pneumonitis (8%), and connective tissue disease ILD (11%). Most elderly subjects (74%) with unclassifiable ILD had an imaging pattern inconsistent with usual interstitial pneumonia (UIP). There were no significant differences in pulmonary function or three-year mortality between non-elderly and elderly subjects combined, or in a subgroup analysis of those with IPF.

Conclusions: While IPF was the single most common diagnosis, the majority of elderly subjects had non-IPF ILD. Our findings highlight the need for every patient with new-onset ILD, regardless of age, to be surveyed for exposures and findings of connective tissue disease. Unclassifiable ILD was common among the elderly, but for most the radiographic pattern was inconsistent with UIP. While the effect of ILD may be more pronounced in the elderly due to reduced global functionality, ILD was not more severe or aggressive in this group.

Introduction

Interstitial lung disease (ILD) encompasses a spectrum of diffuse fibrotic and inflammatory parenchymal injuries. Idiopathic pulmonary fibrosis (IPF) is the ILD most closely related to aging: onset before age 50 is rare, and the incidence of IPF increases with age.(1) Further, IPF is associated with telomerase mutations, indicating it may be related to premature aging.(2, 3) However, beyond the association of IPF and aging, the epidemiology of other forms of ILD in the elderly is not known.

Currently in the United States, 14% of the population is 65 years or older, and at age 65 the average life expectancy is 19.3 years.(4) With population aging, ILD in the elderly is increasingly encountered in clinical practice. In addition, age-related considerations have implications for ILD care. Compared to younger patients, the risks of surgical lung biopsy and immunosuppression are higher for elderly patients.(5-7) Age may also have an impact on survival in ILD. In a large IPF cohort, older age at disease presentation was associated with decreased survival.(8) However, it is not known if ILD is more aggressive at the extremes of age, or if age-related co-morbidities contribute to poor outcomes. In this prospective study of ILD, we sought to define the diagnoses, clinical characteristics, and outcomes of patients who were elderly at the time of ILD presentation.

Methods

This study was approved by the institutional review board of the University of Pennsylvania (protocol number 817689) and is HIPPA compliant. Between 2012 and 2016, patients seen at a tertiary ILD clinic associated with a university-based hospital in the mid-Atlantic United States were serially recruited for study participation, and enrolled via informed consent. As a referral center for a second opinion or consideration of lung transplant, many patients had had their disease for years before the first clinic

visit. Age of ILD onset was therefore defined as the age at which chest imaging first demonstrated ILD, even if onset was before the first visit to our clinic. While a universally accepted definition for "elderly" is lacking, age ≥ 65 is generally considered elderly.(9, 10) We used a more conservative age cut-off of 70 to define elderly for our study. Subjects between 18 and 69 years old comprised our non-elderly cohort.

Testing

Chest computed tomography (CT) imaging obtained near the time of the first clinic visit was reviewed by a thoracic radiology expert in ILD and blinded to clinical details. Surgical lung biopsies, explanted lungs, and autopsy samples were reviewed by a pulmonary pathologist with expertise in ILD. Pulmonary function testing (PFT) and a 6-minute walk test performed near the time of CT imaging were interpreted according to established criteria.(11) When available, results from yearly follow-up PFT and walk tests were also recorded. A decline in lung function was defined as a 10% or greater decrease in the forced vital capacity (FVC), or a 15% or greater decrease in the diffusion capacity (DLCO) in one year. Hypoxemia was defined by the need for supplemental oxygen, and/or a saturation < 90% on room air. Study-termination outcomes included death or lung transplantation.

Clinical review

All subjects underwent a detailed history and physical exam with an emphasis on features discriminating between causes of ILD. ILD diagnoses were established by a multi-disciplinary consensus review including at least two pulmonologists expert in ILD, a thoracic radiologist, and a pulmonary pathologist.(12) IPF was diagnosed according to ATS/ERS/JRS/ALAT criteria.(13) Hypersensitivity pneumonitis was most often established by supportive histopathology in the setting of consistent clinical features. For subjects unable to undergo lung biopsy, a suggestive clinical presentation with an exposure history and imaging features typical for hypersensitivity pneumonitis established the diagnosis. Sarcoidosis was diagnosed according to ATS/ERS/WASOG criteria, and only subjects with interstitial

disease were included in our ILD cohort.(14) A clinical diagnosis of connective tissue disease (CTD) with consistent imaging or histopathology for CTD-ILD estabished this diagnosis. In accordance with society statements on the diagnosis of idiopathic interstitial pneumonias and IPF, unclassifiable ILD was subtyped into categories of (a) inadequate data, (b) discordant data, or (c) "possible usual interstitial pneumonia (UIP)", with radiographic features suggestive of UIP but lacking honeycombing and without biopsy for further assessment.(13, 15) ILD due to chronic aspiration was diagnosed by imaging findings of lower lobe bronchiolitis with documented tracheal aspiration on a barium swallow study, and without an alternative diagnosis to better account for ILD.

Statistical analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the University of Pennsylvania.(16) Comparisons between groups were made using a chi-square test for categorical data, and a one-way analysis of variance for continuous data. For all tests, a p-value < 0.05 determined significance. Data analysis was performed using STATA software (statacorp version 13.1).

Results

Demographics

Of the 327 subjects enrolled, 80 (24%) were elderly. Nearly all elderly subjects were white (94%) and most were male (68%) (Table 1). The non-elderly group was significantly more diverse. Surgical lung biopsies were uncommon (9%) among the elderly.

ILD subtypes as a function of age

The relative incidence of ILDs changes with age (Figure 1a). Sarcoidosis and CTD-ILD accounted for a large percentage of ILD in younger individuals. In the elderly, there were no new cases of sarcoidosis, yet otherwise a variety of ILDs were encountered in this group (Figure 1b). While unclassifiable disease (45%) and IPF (34%) were most common, the burden from CTD-ILD (11%) and hypersensitivity pneumonitis (8%) were also significant. Other causes accounted for 3% of ILD in the elderly, and included one case each of asbestosis and chronic aspiration.

It is often suggested that many cases of unclassifiable ILD in the elderly represent undiagnosed IPF. However, in our cohort, only 26% of elderly subjects with unclassifiable ILD had imaging features consistent with "possible UIP". Of the remainder, 59% had inadequate or non-specific data, and 15% had discordant data. In conjunction with a CT scan not diagnostic of UIP, lack of a surgical lung biopsy was the primary reason data was inadequate, where only 1 out of 20 of these elderly subjects had undergone a surgical lung biopsy. In contrast, all subjects had undergone a basic exposure and review of systems survey, and most (78%) had undergone a serologic assessment, reducing the likelihood of connective tissue disease and hypersensitivity pneumonitis as causes of ILD in this group.

Disease severity

Nearly all subjects (93%) had PFT data to review, and all subjects in the study were assessed for hypoxemia. Functional deficits in lung function and rates of hypoxemia were similar between the two age groups (Figure 2). Results from a 6-minute walk test were available for 235 subjects (72%). The elderly cohort had a lower average walk distance (320 meters vs. 370 meters, p=0.02), and was significantly more likely to be hypoxemic (40% vs. 26%, p=0.01) compared to the non-elderly cohort.

To evaluate the effect of age in a more disease-specific fashion, indices of disease severity for elderly and non-elderly subjects with IPF were compared in a subgroup analysis. Nearly all subjects (96%) with IPF had PFT data, and most (82%) had walk test data to review. No significant differences in FVC (p=0.50), DLCO (p=0.42), walk distances (p=0.11), or rates of hypoxemia (p=0.29) were noted between non-elderly and elderly subjects with IPF (Table 2).

Long-term outcomes

At the time of this study, nearly all subjects (98%) had had their ILD for at least a year. Of those, 195 had one-year FVC data available for review. Fewer subjects (43%) had one-year DLCO data. Among those with follow-up data, the frequency of pulmonary function decline in the first year was similar in the elderly and non-elderly (Table 3). The frequency of pulmonary function decline in IPF in particular also was similar in the elderly and non-elderly (Table 3).

Among the 251 subjects who had been diagnosed with ILD three or more years prior to the time of this study, 151 subjects were confirmed alive, 8 had died, and 6 had undergone lung transplant within 3 years of their diagnosis. Eighty-six subjects were lost to follow-up or did not have full clinical data to review at 3 years. Only a minority (17%) of subjects in our cohort who have undergone lung transplant was elderly at the time of disease onset. Excluding subjects with insufficient data, 3-year mortality rates were not different between elderly and non-elderly subjects (p=0.79) (Table 3). While 3-year mortality rates were higher for those with IPF compared to non-IPF ILD (13% vs. 6%), IPF mortality rates were not higher for elderly compared to non-elderly subjects (p=0.38) (Table 3).

Discussion

Most elderly subjects with new-onset ILD were men, and nearly all were white. Historically, higher incidences of smoking and occupational exposures have predisposed men more than women to certain ILDs. It is possible that these factors contribute to the male predominance observed in our elderly cohort. Similar to findings in previous reports on the epidemiology of IPF, no elderly subjects with IPF in our study were black and only a small percentage of all elderly subjects with ILD were black.(17, 18) Yet, by recent census data, blacks account for 6.1% of people 65 and older in the United States, and a sizeable percentage of patients served by our institution are black. The reason for the disproportionately low prevalence of IPF among blacks is unknown.

Due to the strong association of IPF with advanced age, it may be assumed that IPF accounts for the majority of new-onset ILD in the elderly. However, our data contradict this assertion, where IPF accounted for only 34% of new-onset ILD in an elderly cohort. Other ILDs, such as unclassifiable ILD not resembling UIP (33%), CTD-ILD (11%), and hypersensitivity pneumonitis (8%), were common among the elderly. Thus, like their non-elderly counterparts, elderly patients with ILD should be surveyed for exposures and for extra-thoracic findings indicative of connective tissue disease.

A radiographic pattern of “possible UIP” is very often found to be UIP if histologic sampling is pursued.(19) Indeed, this may be particularly the case for elderly subjects, where Fell and colleagues found that nearly all patients older than 70 with fibrotic reticulations but lacking radiographic honeycombing had UIP on histopathology, and were given a diagnosis of IPF.(20) However, among our elderly subjects with unclassifiable ILD, only a minority (26%) met radiographic criteria for “possible UIP”. Our interest, therefore, centers around the 74% of elderly subjects with unclassifiable ILD who had a radiographic pattern inconsistent with UIP. While we suspect that many of these subjects have a disease other than IPF, it is known that some patients with radiographs inconsistent with UIP will be

given a diagnosis of IPF if lung biopsies are interpreted as diagnostic of UIP. In a study of patients pre-selected for having biopsy-established UIP, nearly a third had a CT pattern inconsistent with UIP.(21) This underscores the necessity for surgical lung biopsy when medically feasible in elderly subjects with unclassifiable ILD, even as the prevalence of UIP among all comers with an imaging pattern inconsistent with UIP is unknown. Given that at least some portion of these patients will have discordant radiographic-histologic UIP, and in light of the recent approval of therapies for IPF, the risk-benefit ratio of undergoing a surgical lung biopsy, even in elderly patients, may shift in favor of biopsy.

Minor “interstitial changes” are commonly identified on CT scans of older patients. In one study, limited-extent peripheral reticulations on CT imaging were noted in 60% of asymptomatic patients older than 75.(22) Therefore, it might be suspected that a large percentage of our unclassifiable ILD represents incidentally identified, clinically irrelevant interstitial findings. However, nearly all of our subjects had objective measures of abnormal lung function. Finally, it is possible that some of the unclassifiable ILD in the elderly represents aspiration related scarring.(23) It is well known that the incidence of aspiration increases with age.(24, 25) It is unclear, however, whether aspiration results in clinically relevant interstitial fibrosis. Further studies to characterize the features and outcomes of unclassifiable disease in the elderly and non-elderly alike are needed.

In general, the impact of diseases is often greater for older compared to younger patients. We were surprised to see that this was largely not the case with ILD in our population. Functional deficits, rates of decline, and mortality were not significantly different between the elderly and non-elderly. While the walk distance was lower in the elderly, this test is an indirect measure of ILD severity, and its

determinants are multi-factorial. Therefore, hypoxemia was the only functional measure directly related to ILD that was worse in the elderly population.

Prior studies have suggested that mortality in patients with IPF is related to age at disease onset.(8) Yet, we found that key measures of disease including lung function, rates of hypoxemia, and long-term outcomes, including mortality, were similar for non-elderly and elderly subjects with IPF. Larger cohort data utilizing updated diagnostic criteria, and with sufficient follow-up periods, will further clarify the effect of age on the disease course in IPF.

There are several limitations of this study. Surgical lung biopsies were rare among our elderly subjects, which may account for the high burden of unclassifiable disease in this age group. The risk-benefit ratio of a surgical lung biopsy in older patients is often unfavorable, where rates of co-morbidities and surgical risks are higher.(5) Not all subjects yet have follow-up data available for review, which limited a full assessment of the natural history of ILD in the elderly. In addition, as a tertiary referral center, the possibility of referral bias is acknowledged. In particular, our cohort may be enriched for patients with atypical features, including atypical radiographic patterns, which will limit the generalizability of our findings. Finally we acknowledge our small sample size as a limitation, which may have influenced the results of our analysis of disease progression. We plan to replicate these findings in a larger population as the study is ongoing.

To our knowledge, this study is the first to characterize the causes and clinical features of ILD in an elderly population. As expected, IPF was the single most commonly diagnosed ILD in the elderly.

However, it was not expected that over half of elderly patients would have an ILD other than IPF, and that a variety of ILDs would be present among this group, including CTD-ILD and hypersensitivity pneumonitis. ILD severity and rates of progression were similar between the elderly and non-elderly, suggesting that a patient's overall functional status and ILD subtype should factor into prognostication more than age. As life expectancy continues to increase, more studies to further clarify the impact and natural history of ILD in the elderly are important.

Table 1 Clinical characteristics of non-elderly and elderly subjects with ILD

Table 2 Disease severity by age groups for all ILD combined and for IPF

Table 3 Outcomes by age groups for all ILD combined and for IPF

Figure 1: Distribution of ILD diagnoses by age. The relative occurrence of ILDs across the full range of ages is demonstrated in Figure 1a. The numbers of ILD diagnoses in the non-elderly and elderly groups are shown in Figure 1b. Sarcoidosis was common among the non-elderly, but there were no cases of new-onset sarcoidosis in the elderly. The proportion of IPF and unclassifiable ILD increased with age. However, new-onset CTD-ILD and hypersensitivity pneumonitis combined also constituted a sizeable minority of ILD in the elderly.

Acknowledgments/Author roles:

Karen Patterson is the guarantor of this manuscript. She has made substantial contributions to the conception and design, and to the acquisition, analysis, and interpretation of data; has drafted the submitted article and all revised documents; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

Rupal Shah has made substantial contributions to the conception and design, and to the acquisition, analysis and interpretation of data; participated in the writing/editing of all submitted drafts of the article; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work

Mary Porteous has made substantial contributions to the conception and design, and to the acquisition, analysis, and interpretation of data; participated in the writing/editing of all submitted drafts of the article; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

Jason Christie has made substantial contributions to the conception and design, and to the analysis and interpretation of data; reviewed the submitted article and all revised documents; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

Carly D'Errico has made substantial contributions to the acquisition, analysis, and interpretation of data; reviewed the submitted article and all revised documents; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

Matthew Chadwick has made substantial contributions to the conception and design, and to the acquisition, analysis and interpretation of data; reviewed the submitted article and all revised documents; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

Matthew Triano has made substantial contributions to the acquisition of data; reviewed/edited the submitted article and all revised documents; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

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Wallace Miller Jr has made substantial contributions to the conception and design, and to the acquisition, analysis and interpretation of data; has drafted the submitted article and all revised documents; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

References

1. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006; 174: 810-816.
2. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, Lawson WE, Xie M, Vulto I, Phillips JA, 3rd, Lansdorp PM, Greider CW, Loyd JE. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 2007; 356: 1317-1326.
3. Snetselaar R, van Moorsel CH, Kazemier KM, van der Vis JJ, Zanen P, van Oosterhout MF, Grutters JC. Telomere length in interstitial lung diseases. *Chest* 2015; 148: 1011-1018.
4. Administration on Aging AfCL, U.S. Department of Health and Human Services. 2012. Available from: http://www.aoa.acl.gov/aging_statistics/profile/2014/docs/2014-Profile.pdf.
5. Falcoz PE, Conti M, Brouchet L, Chocron S, Puyraveau M, Mercier M, Etievent JP, Dahan M. The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital death in 15,183 patients requiring thoracic surgery. *J Thorac Cardiovasc Surg* 2007; 133: 325-332.
6. Meier-Kriesche HU, Ojo A, Hanson J, Cibrik D, Lake K, Agodoa LY, Leichtman A, Kaplan B. Increased immunosuppressive vulnerability in elderly renal transplant recipients. *Transplantation* 2000; 69: 885-889.
7. Utz JP, Ryu JH, Douglas WW, Hartman TE, Tazelaar HD, Myers JL, Allen MS, Schroeder DR. High short-term mortality following lung biopsy for usual interstitial pneumonia. *Eur Respir J* 2001; 17: 175-179.
8. King TE, Jr., Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001; 164: 1171-1181.
9. Williams MA, Maresh CM, Esterbrooks DJ, Harbrecht JJ, Sketch MH. Early exercise training in patients older than age 65 years compared with that in younger patients after acute myocardial infarction or coronary artery bypass grafting. *Am J Cardiol* 1985; 55: 263-266.
10. Jennifer M. Ortman VAV, Howard Hogan. An Aging Nation: The Older Population in the United States Population Estimates and rojections. 2014.
11. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. General considerations for lung function testing. *Eur Respir J* 2005; 26: 153-161.
12. Flaherty KR, King TE, Jr., Raghu G, Lynch JP, 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004; 170: 904-910.
13. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Jr., Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ, Fibrosis AEJACoIP. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788-824.
14. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous

Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999; 160: 736-755.
15. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D, Pneumonias AECoII. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733-748.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377-381.
17. Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon J, Sprunger D, Brown KK. Ethnic and racial differences in the presence of idiopathic pulmonary fibrosis at death. *Respir Med* 2012; 106: 588-593.
18. Cogan JD, Kropski JA, Zhao M, Mitchell DB, Rives L, Markin C, Garnett ET, Montgomery KH, Mason WR, McKean DF, Powers J, Murphy E, Olson LM, Choi L, Cheng DS, Blue EM, Young LR, Lancaster LH, Steele MP, Brown KK, Schwarz MI, Fingerlin TE, Schwartz DA, Lawson WE, Loyd JE, Zhao Z, Phillips JA, 3rd, Blackwell TS. Rare variants in RTEL1 are associated with familial interstitial pneumonia. *Am J Respir Crit Care Med* 2015; 191: 646-655.
19. Chung JH, Chawla A, Peljto AL, Cool CD, Groshong SD, Talbert JL, McKean DF, Brown KK, Fingerlin TE, Schwarz MI, Schwartz DA, Lynch DA. CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis. *Chest* 2015; 147: 450-459.
20. Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, Gross BH, Myers J, Travis WD, Colby TV, Toews GB, Flaherty KR. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2010; 181: 832-837.
21. Yagihashi K, Huckleberry J, Colby TV, Tazelaar HD, Zach J, Sundaram B, Pipavath S, Schwarz MI, Lynch DA, Idiopathic Pulmonary Fibrosis Clinical Research N. Radiologic-pathologic discordance in biopsy-proven usual interstitial pneumonia. *Eur Respir J* 2016; 47: 1189-1197.
22. Copley SJ, Wells AU, Hawtin KE, Gibson DJ, Hodson JM, Jacques AE, Hansell DM. Lung morphology in the elderly: comparative CT study of subjects over 75 years old versus those under 55 years old. *Radiology* 2009; 251: 566-573.
23. Cardasis JJ, MacMahon H, Husain AN. The spectrum of lung disease due to chronic occult aspiration. *Ann Am Thorac Soc* 2014; 11: 865-873.
24. Poh CH, Navarro-Rodriguez T, Fass R. Review: treatment of gastroesophageal reflux disease in the elderly. *Am J Med* 2010; 123: 496-501.
25. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. *Chest* 2003; 124: 328-336.